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EXAMINER	
SCHLAPKOHL, WALTER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,761	ERLANDER ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	WAS

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-38,42,49,50 and 52-66* is/are pending in the application.

4a) Of the above claim(s) *49 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-38,42 and 52-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :3/24/05, 6/8/05, 7/25/05 & 5/26/06.

DETAILED ACTION

Receipt is acknowledged of the papers filed 1/16/2007, 3/5/2007 and 3/27/2007. Claims 6-38, 42, 49-50 and 52-66 are pending. Claims 49-50 are withdrawn. Claims 6-38, 42 and 52-66 are under examination in the instant Office action.

Election/Restrictions

Applicant's election with traverse of Group I (claims 7-11, 15-19, 22, 24-28, 31, 33-35, 38, 42 and 49-63) in the reply filed on 1/16/2007 is acknowledged. Applicant's election of the combination of HOXB13 and IL17BR expression as a ratio is also acknowledged.

Applicant's traversal of the restriction requirement is on the ground(s) that the separation of the claims in Groups I, II and V appears to reflect a failure to recognize the presence of genus claims. Applicant further asserts that, contrary to the restriction requirement, the sequences featured in claims 49-50 and 52-57 are all either those of HOXB13 or IL17BR as encompassed by the genus claims. Accordingly, Applicant argues, the attempt by Examiner to assert that the sequences are 'different and distinct' is an improper attempt to avoid the

standards reflected in *In re Weber* (580 F.2d 455) and *In re Haas* as well as the discussion at MPEP 803.02.

Applicant's arguments have been carefully considered and have been found persuasive in part and rendered moot in part by the rejoinder of Groups I-V. Applicant's arguments with regard to the presence/recognition of genus claims are found persuasive. Examiner acknowledges for the record that claims 6-9, 14-17, 22-26, 31-34, and 58-60 are genus claims. Furthermore, Applicant's election of SEQ ID NOS: 6 and 1 as representative HOXB13 and IL17RB sequences, respectively, is acknowledged as is Applicant's assertion that the sequences featured in claims 49-50 and 52-57 are all either those of HOXB13 or IL17RB as encompassed by the genus claims. Because the claimed SEQ IDS are dependent upon genus claims, Examiner agrees to rejoin the recited sequences upon the allowance of the genus claims(s).

The requirement to the (now) properly presented election of species with regard to the sequences of claims 49-50 and 52-57 is still deemed proper as is the restriction requirement for election of one or one combination of genes selected from HOXB13 and IL17BR. The restriction requirement is therefore made FINAL.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/504,087, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application No. 60/504,087 as originally filed does not provide support for the invention as now claimed: "[a] method to determine clinical outcome of a breast cancer afflicted subject, said method comprising assaying a sample of breast cancer cells from said

subject for the ratio of HoxB13 and IL17BR expression levels" (claim 6); or "[a] method of determining prognosis of a subject having breast cancer if treated with an antiestrogen agent against breat cancer…said method comprising: assaying for the ratio of HoxB13 and IL17BR expression levels in a breast cancer sample from said subject" (claim 14); or "[a] method to determine therapeutic treatment for breast cancer patient based upon said patient's expected response or lack of response to treatment with an antiestrogen agent against breast cancer, said method comprising determining an expected response or non-response to treatment with an antiestrogen agent against breast cancer for said patient by assaying a sample of breast cancer cells from said patient for the ratio of HoxB13 and IL17BR expression levels according to claim 6; and selecting the appropriate treatment for said patient" (claim 23). The 60/504,087 application does not provide sufficient blazemarks nor direction for the instant method steps encompassed by the above-mentioned limitation, as currently recited. The instant claims now recite a limitation, which was not clearly disclosed in the prior application as filed. Such a limitation recited in the present claims, which did not appear in the prior application, introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112.

Therefore the benefit of priority is granted only to the date of filing of Application No. 10/727,100 of which this application is a continuation-in-part: 12/2/2003.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the specification that lack sequence identifiers (see Appendix listing of sequences presented as GenBank accession numbers). Applicant is required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F. R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Specification

The disclosure is objected to because of the following informalities: the disclosure comprises numerous tables which

are not labeled with a number (see, e.g., tables on 31-34, 39-41, etc.).

Appropriate correction is required.

Claim Objections

Claim 9 is objected to because of the following informalities: claim 9 recites "[t]he method of claim 6 wherein said sample of breast cancer cells is ER+" in lines 1-2; the abbreviation "ER+" should be spelled out at its first occurrence in the claims.

Similarly, claim 11 recites the term "quantitative PCR" in line 3; this term should be spelled out at its first occurrence in the claims.

Claims 32-38, 42 and 59-60 are objected to because they comprise non-elected subject matter, i.e. the claims are drawn to embodiments wherein HoxB13 or IL17BR sequences are used alone or in combination with sequences other than the combination of HoxB13 and IL17BR sequences.

Claim 36 is also objected to because it is accompanied by the status identifier "(Previously presented)" and should instead have been accompanied by the status identifier "(Currently amended)".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8, 14, 16, 23, 25 & 32-33, and therefore dependent claims 7, 9-13, 15, 17-22, 24, 26-31, 34-38, 42 & 52-66, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 6 recites "[a] method to determine clinical outcome of a breast cancer afflicted subject if treated with an antiestrogen agent against breast cancer, said method comprising assaying a sample of breast cancer cells from said subject for the ratio of HoxB13 and IL17BR expression levels" in lines 1-4 (emphasis added). Claim 6 is vague and indefinite in that the metes and bounds of an "antiestrogen agent" are unclear. Applicant's specification lacks a definition for this term, Applicant's use of the term seems to include agents which modulate estrogen receptors in such a way that they are either downregulated or upregulated, yet the term implies that the agent works in opposition to the function of estrogen.

Similarly, claims 8, 14, 16, 23, 25 and 32-33 recite the term "antiestrogen agent" and are therefore vague and indefinite as explained for claim 6, above.

Claim 23 recites "[a] method to determine therapeutic treatment for breast cancer patient based upon said patient's expected response or lack of response to treatment with an antiestrogen agent against breast cancer, said method comprising determining an expected response or non-response to treatment with an antiestrogen agent against breast cancer for said patient by assaying a sample of breast cancer cells from said patient for the ratio of HoxB13 and IL17BR expression levels according to claim 6; and selecting the appropriate treatment for said patient" in lines 1-7 (emphasis added). Claim 23 is vague and indefinite in that the metes and bounds of "the appropriate treatment" are unclear. Which treatments are considered by Applicant to be "appropriate"? Even if "appropriate" treatments are limited to therapeutic treatments as suggested by the preamble, which therapeutic treatments are considered by Applicant to be "appropriate"? The term "appropriate treatment" is not defined in the claims or in the specification and one or ordinary skill in the art would not be apprised of its scope.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-38, 42 and 52-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 6-38, 42 and 52-66 encompass sequences with a genus of "HoxB13" and "IL17BR" sequences which are critical or essential to the practice of the invention but are not supported by the disclosure. The GenBank Accession numbers, UniGene cluster numbers and I.M.A.G.E. Consortium numbers taught in the specification as HOXB13 and IL17BR sequences refer to entries in an electronic database which is subject to change over time. "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication which patent or patent application publication does not itself incorporate such essential material

by reference. In the instant case, the claims are, in effect, incorporating the sequences associated with GenBank Accession numbers, UniGene cluster numbers and I.M.A.G.E. Consortium numbers by reference to the entries in the electronic databases. While the specification teaches that at least the GenBank sequences have been included in the Appendix, it remains unclear which sequences of those that have been incorporated by reference are presently disclosed in the specification and/or are present in the sequence listing. Accordingly, insofar as Applicant's invention includes sequences which have only been disclosed by way of reference to the GenBank Accession numbers, Unigene numbers and I.M.A.G.E. consortium numbers, Applicant has not provided the features that are critical or essential to the practice of the claimed invention.

If Applicant seeks to correct the sequences improperly incorporated by reference, Applicant must include a complete sequence listing as well as comply with the rest of the requirements of 37 CFR 1.821 through 1.825 (see above). However, this is NOT an invitation for Applicant to submit sequences that would be considered new matter. It is further noted that the nature of the noncompliance with the requirements of 37 C.F. R. 1.821 through 1.825 did not preclude examination on the merits in this case.

Claims 6-38, 42 and 52-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method of determining the clinical outcome of a breast cancer afflicted subject if treated with an antiestrogen agent wherein the method comprises assaying a sample of breast cells for the ratio of HOXB13 and IL17BR expression levels. Some claims are further limited to such methods wherein the antiestrogen agent is either a selective estrogen receptor modulator (SERM), a selective estrogen receptor downregulator (SERD) or an aromatase inhibitor (AI). Other claims are further limited to such methods wherein protein expression levels are determined by detection of the presence of proteolytic fragments of HOXB13 and IL17BR in the blood of the patient or in epithelial cells enriched form the blood of said patient. Still other claims are further limited to such methods wherein HOXB13 and IL17BR expression are determined by assay for HOXB13 or IL17BR expression in breast *cancer* cells. The claims

encompass the use of any antiestrogen agent, any breast cell or blood sample and any HOXB13 and IL17BR sequence such that clinical outcome of a human having breast cancer if treated with an antiestrogen agent can be determined and/or an appropriate treatment can be selected. The claims do not provide any structural information with regard to the antiestrogen agents which can be used in combination with any breast cells and any IL17BR and HOXB13 sequences (nucleic acid, amino acid, and/or methylated) such that the method can be performed successfully. Thus, the rejected claims comprise a set of compounds, biological samples and sequences that are defined by their function within the recited methods.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification provides generic teachings with regard to antiestrogen agents such as that found on page 15, lines 24-26: "Preferred SERMS of the invention are those that are antagonists of estrogen in breast tissues and cells, including those of breast cancer.

Non-limiting examples of such include TAM, raloxifene, GW5638, and ICI 182,780." Example 1 teaches the use of ER+ breast cancer tumor specimens which were frozen and formalin-fixed paraffin-embedded at the time of initial diagnosis.

No description is provided of an antiestrogen agent other than tamoxifen used in the claimed methods.

No description is provided of breast cells and/or blood samples other than frozen tumor samples which were used in the claimed methods.

No description is provided of the IL17BR and HOXB13 nucleic sequences used in the examples.

No description is provided of the claimed methods wherein protein or proteolytic fragments were used to assess the ratio of HOXB13 and IL17BR expression.

No description is provided of the claimed methods wherein methylation of HOXB13 and IL17BR sequences was used to assess the ratio of HOXB13 and IL17BR expression, much less such a method wherein said ratio was used to diagnose the outcome of a breast cancer patient treated with any antiestrogen agent.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of one antiestrogen agent, one type of

cell/biological sample, and a few different unmethylated IL17BR and HOXB13 nucleic acid sequences. The results are not necessarily predictive of any other antiestrogen agent or any other biological/cell sample or any other indicator of a IL17BR:HOXB13 ratio which was or could be used in such a method. Thus, it is impossible to extrapolate from the example(s) described herein those antiestrogen agents/cell samples/nucleic acid molecules/proteolytic fragments that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of IL17BR or HOXB13 sequences capable of use in a method of determining clinical outcome breast cancer if treated with any antiestogen agent as determined by the ratio of HOXB13 and IL17BR expression within any breast cell. In fact, in an article published post-filing, Ma et al teach that "[l]ittle is known about the relevance of HOXB13 in breast cancer biology" (*Cancer Cell* **5**:607-616, 2004; IDS Ref BI; see entire document, especially page 613, 1st column, first full paragraph). Ma et al further teach that expression levels of estrogen receptor and progesterone receptor are currently the best predictors of

tamoxifen response in the clinical setting (page 607, sentence bridging first and second columns).

Given the very large genus of antiestrogen agents, cell samples, nucleic acid molecules (methylated and otherwise) and proteolytic fragments encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the antiestrogen agents, cell samples, nucleic acid molecules (methylated and otherwise) and proteolytic fragments capable of fulfilling the claim limitations of claims 6-38, 42 and 52-66, the skilled artisan would not have been able to describe the broadly claimed genus of antiestrogen agents, cell samples, nucleic acid molecules (methylated and otherwise) and proteolytic fragments that together can be used to determine clinical outcome of a patient as required by the instant claims. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those antiestrogen agents, cell samples, nucleic acid molecules (methylated and otherwise) and proteoltyic fragments that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 6-38, 42 and 52-66.

Claims 6-38, 42 and 52-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The instant claims are drawn to a method of determining the clinical outcome of a breast cancer afflicted subject if treated with an antiestrogen agent wherein the method comprises assaying a sample of breast cells for the ratio of HOXB13 and IL17BR expression levels. Some claims are further limited to such methods wherein RNA expression levels are measured by mRNA amplification and/or quantitative PCR. Other claims are further limited to such methods wherein protein

expression levels by detection of there presence in the blood of said subject or in breast cancer epithelial cells enriched from the blood of said subject. Still other claims are further limited to such methods wherein HOXB13 and IL17BR expression are determined by assay for HOXB13 or IL17BR nucleic acid methylation. Some claims are further limited to such a method wherein the cells are breast *cancer* cells. The invention is complex in that it involves measuring the expression levels of two genes in a breast cell sample such that the ratio of their expression levels alone is indicative of a clinical outcome/prognosis/appropriate treatment course. The nature of the invention requires knowledge of a correlation between the expression of any HOXB13 and IL17BR sequence in any breast cell sample and the predisposition of a patient from which the sample was taken to a given clinical outcome. The nature of the claimed invention requires that such a correlation can be made by using a sample comprising any given breast cell.

Breadth of the claims: The claims are extremely broad in that they encompass the diagnosis of any clinical outcome of any breast cancer afflicted subject. The assay comprises the measurement of any HOXB13 and IL17BR sequence from any sample of breast cells. The claims also encompass the measurement of HOXB13 and IL17BR levels at any time in the course of breast

cancer and the determination of a prognosis and/or the selection of any "appropriate" treatment based upon the information obtained from any ratio of HOXB13 and IL17BR expression levels. In other words, the gene expression levels can differ by any amount. The large breadth of the claims exacerbates the complexity of the invention.

Guidance of the specification/The existence of working examples: The specification provides a number of HOXB13 and IL17BR sequences and teaches (by way of example) that "any sequence, or unique portion thereof, of the following IL17BR sequence, identified by AF208111 or AF208111.1, may be used in the practice of the invention" and goes on to disclose the IL17BR sequence of SEQ ID NO: 3 (see pages 34, lines 2-4 and SEQ ID NO:3 on page 34-35). Similarly, the specification teaches, also by way of example, that "any sequence encoding all or part of the protein encoded by any IL17BR sequence disclosed herein may be used" (page 29, lines 4-10). In Example 1 the specification teaches that a 22,000-gene high-density oligonucleotide microarray was used to determine gene expression patterns from 60 ER+ breast cancer patients who were uniformly treated with tamoxifen (see page 60, line 20 to page 61, line 14). The IL17BR and HOXB13 oligonucleotide sequences used in the microarray are undisclosed. In example 2, the specification

teaches that from the resulting data set, 5,475 genes were selected for further analysis and that using this reduced dataset, a t-test was performed on each gene comparing "the tamoxifen responders and non-responders, leading to identification of 19 differentially expressed genes at the P value cutoff of 0.001 (Table 2)", including HOXB13 and IL17RB (see page 65, lines 5-15). Then, to further refine the analysis, the specification teaches that Applicant reanalyzed the same cohort following laser-capture microdissection of tumor cells within each tissue section and 9 differentially expressed gene sequences were identified with $P<0.001$, again including HOXB13 and IL17BR (see page 66, lines 2-6 and Table 3). Indeed, HOXB13, IL17BR, and CACNA1D expression levels were found to be significantly correlative in both the LCM and whole tissue section samples (see, e.g., page 67, lines 3-10). The specification further concedes that "…these three genes have *potential utility* for predicting clinical outcome of adjuvant tamoxifen therapy" (page 68, lines 6-7; emphasis added). Finally, the specification discloses that the HOXB13 and IL17BR expression ratio is a "strong independent predictor of treatment outcome *in the setting of adjuvant tamoxifen therapy*" (see, e.g., page 70, lines 5-7; emphasis added).

The specification does not teach the use of such a ratio outside the setting of adjuvant tamoxifen therapy.

The specification does not teach what is meant by the terms "responders" and "non-responders" although the specification designates patient status as either "1" (recurred) or "0" (disease-free) in Table 1, pages 63-65, to indicate response to tamoxifen adjuvant therapy. Moreover, the specification does not teach whether patients who remained disease-free during the entire follow up period would have been cured by surgery alone, nor does the specification teach how such a determination could be made with the data set provided.

The specification does not teach what levels of expression of HOXB13 and IL17BR sequences are required such that the ratio is indicative of any given clinical outcome, even response to adjuvant tamoxifen therapy.

The specification does not provide any statistical analysis of the expression level of HOXB13 and IL17BR sequences or even a ratio of such expression levels for patients who were NOT treated with tamoxifen.

The specification does not differentiate which HOXB13/IL17BR expression levels are indicative, or even teach how to use HOXB13 and IL17BR ratios, such that any prognosis of

a subject with ER+ breast cancer can be determined and an appropriate treatment can be selected.

State of the prior art: The literature does report an example of a gene expression profile which is predictive of "a short interval of distant metastases" in breast cancer referred to a as a "poor prognosis" signature (van't Veer et al, *Nature* **415**:530-536, 2002; IDS Ref BH; see entire document, especially the Abstract). This signature was derived from a test of 98 primary breast cancers from node-negative patients and consisted of 70 genes including those regulating cell cycle, invasion, metastasis and angiogenesis (ibid and page 530, 2nd column, 1st full paragraph). van't Veer et al also teach that, prior to their study, none of the signatures of breast cancer gene expression reported allowed for patient-tailored therapy strategies" (see page 530, 1st column, 1st paragraph). Moreover, Applicant concedes in the specification that while estrogen receptor and progesterone receptor status is a powerful predictor of response to tamoxifen, "25% of ER+/PR+ tumors, 66% of ER+/PR- cases and 55% of ER-/PR+ cases fail to respond, or develop early resistance to tamoxifen, through mechanisms that remain largely unclear" (see, e.g., page 4, liens 11-15). Thus, the state of the art is underdeveloped with respect to the use of a gene expression profiles generally (much less the use of

only IL17BR and HOXB13 sequences) to predict breast cancer outcome.

The prior art also does not appear to offset the deficiencies of the instant specification in that it does not describe the use or even the correlation of methylated HOXB13 and IL17BR genes with breast cancer, much less the use of a ratio of expression of HOXB13 and IL17BR as determined by the methylation status of said genes such that the ratio would be predictive of clinical outcome of a patient treated with any antiestrogen agent. The unpredictability with regard to the use of methylation to determine cancer prognosis is taught in the prior art by Yamamoto et al (*Genes, Chromosomes & Cancer* **33**:322-325, 2002) who analysed the methylation status of a series of genes including p24, MLH1 and APC in colorectal cancer samples from HNPCC families and found that there was "no significant association between DNA methylation of each CpG island and clinicopathologic parameters of the tumors in each tumor group…" (see page 323, 2nd column 2nd full paragraph). Van Rijnsoever et al (*Gut* **51**(6):797-802, 2002) also teach the use of p16, MDR1 and MINT-2 in characterizing CRC tumors but note that "little is known of the prognostic significance of CpG island methylation in CRC" (see page 801, 1st column, 1st full paragraph). Furthermore, van Rijnsoever et al also teach that no prognostic

significance for p16 methylation alone was found (ibid). With regard to HOXB13 and IL17BR methylation specifically, post-filing art teaches that HOXB13 methylation has been correlated with renal cell carcinoma but the methylation status of HOXB13 has yet to be confirmed as a diagnostic marker (Okuda et al. *Oncogene* **25**:1733-1742, 2006). No prior art appears to exist for the use of IL17BR methylation status as a predictor of IL17BR expression.

Predictability of the art/Amount of experimentation necessary: The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art by Wu (*J. Pathol.* **195**(1):53-65, 2001.). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 - Discussion). Additionally, post-filing art

reveals that most gene association studies are typically wrong. Lucentini (*The Scientist*, page 20, Dec. 20, 2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (middle column, 1st full paragraph).

The lack of predictive success of gene expression studies may, in part, be due to the fact that increased mRNA is not always indicative of protein expression levels. Chen et al (*Molecular and Cellular Proteomics* **1**:304-313, 2002) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (page 304) and "it is not possible to predict overall protein expression

levels based on average mRNA abundance in lung cancer samples" (pages 311-312).

Most significantly, post-filing art does report the use of HOXB13 and IL17BR to attempt to predict clinical outcome in breast cancer patients treated with tamoxifen (Ma, et al. *Cancer Cell* **5**:607-616, 2004; IDS Ref BI). This study also discloses a study in which gene expression profiles of ER+ primary breast cancers treated with adjuvant tamoxifen therapy were generated (see entire document, especially the Abstract). However, Ma et al conclude that "[t]he observation that a simple expression ratio of two genes, HOXB13:IL17BR, accurately predicts tumor recurrence in adjuvant tamoxifen-treated patient with early-stage ER-positive breast cancer is limited by the size of patient cohorts" and that it "will require confirmation in a large population-based cohort" (paragraph bridging pages 612-613). Moreover, Ma et al concede that "it remains to be determined whether this two-gene ratio predicts a tumor's response to tamoxifen or its intrinsic aggressiveness, or both" and that a "similarly case-matched cohort of untreated patients will be required to address this issue" (ibid). This level of unpredictability is exacerbated by the fact that "little is known about the relevance of HOXB13 in breast cancer biology", and further that "[l]ittle information exists in the literature

linking IL17BR to breast cancer" as further taught by Ma, et al (page 611, 2nd column, 1st full paragraph and page 613, 1st column, 1st full paragraph).

Given the complex nature of invention and the underdeveloped state of the art at the time of filing, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. First, one would have to establish that HOXB13 and IL17BR sequences were predictive of clinical outcome in patients NOT treated with tamoxifen. Second, one of ordinary skill in the art would then have to determine which levels of HOXB13 and IL17BR expression were indicative of any given clinical outcome/diagnosis/treatment course selection. Such testing is not routine and would require a burdensome and undue amount of trial-and-error experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re*

Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 32-37, 42 and 59-60 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/089,097. Although the conflicting claims are not identical, the instant claims anticipate claim 1 of copending Application No. 11/089,097 because both claim sets encompass the measurement of HOXB13 and IL17BR expression levels in a cell sample. Although claim 1 of the 11/089,097 application does not recite any of the features of claims 33-37, 42 and 59-60 such as measurement of HoxB13 and IL17BR expression levels from cell samples obtained by minimally invasive techniques or through the use of nucleic acids prepared by mRNA amplification, such limitations are taught within the specification of the 11/089,097 application and as such would be obvious

variations/embodiments of claim 1 and are properly rejected on the ground of nonstatutory obviousness-type double patenting.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 6-38, 42 and 52-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-23, 25-33, 35-40, 42-44, 46-47, 54-56, 58-63 and 65-73 of copending Application No. 10/727,100. Although the conflicting claims are not identical, the instant claims anticipate the claims of the 10/727,100 application because both claim sets encompass the measurement of HOXB13 and IL17BR expression levels in ER+ breast cancer samples such that either a clinical outcome or a prognosis can be determined, or such that a therapeutic treatment can be selected. Both sets of claims are drawn to such methods wherein the clinical outcome is determined if the patient is treated with an estrogen receptor modulator/antiestrogen compound/tamoxifen. Both sets of claims are drawn to such methods wherein the nucleic acids are prepared either by mRNA amplification or quantitative PCR. Moreover, both sets of claims are drawn to such measurements wherein the

samples were procured by either fine needle aspiration or microdissection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Joseph Woitach can be reached at (571) 272-0739.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

June 4, 2007

DAVID GUZO
PRIMARY EXAMINER